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EFFECTS OF CHOLINERGIC PERTURBATIONS ON NEUROMOTOR - COGNITIVE PERFORMANCE

Annual Report

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September 1988

Supported by

U.S. ARMY MEDICAL RESEARCH AND DEVELOPMENT COMMAND
Fort Detrick, Frederick, Maryland, 21701-5012

Contract No. DAMD17-85-C-5207

Duke University Medical Center
Durham, North Carolina 27710

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Foreword

For the protection of human subjects the investigators have adhered to policies of applicable Federal Law 45CFR46.

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Introduction

In a continuing effort to document, systematically, the dose dependent effect of atropine in man (in the absence of an organophosphate challenge), we have evaluated a new series of cognitive-neuromotor tasks. In the confusion of military encounters in a combat environment, large numbers of personnel could potentially self-administer 2.0-6.0 mg of atropine when there is a misinterpretation of events and/or there is an over-reaction resulting in multiple injections within a short period of time. Indeed, multiple doses of atropine alone may be utilized rationally as a prophylactic under certain conditions.

This research document is aimed at specific drug-induced changes at the neuromotor, cognitive and physiological level, has resulted in a series of studies utilizing recently developed tests comparing the atropine sensitivity of these new tests and earlier studies evaluated in our lab. We anchored the assessment of the new tasks to a performance task, subcritical tracking, previously demonstrated to have sensitive, dose dependent, and concentration dependent impairment with atropine. This task involves the utilization of a computer generated "instability algorithm" which controls a TV cursor that the subject is required to keep in the center of the TV screen by turning an automobile steering wheel (with appropriate transducers that allow the wheel to control the cursor). In our studies we attempted to factor out the autonomic responses of the eye as a major contributing factor. All tasks were projected onto a large screen TV in order to overcome any of the atropine effects of mydriasis and cycloplegia. Large screen tasks were necessary to examine the specific drug effects in the absence of the contribution of atropine-induced difficulties with accommodation and near vision. All tasks were also conducted in a dimly lit room to avoid the potential effects of photophobia or lack of pupil adaptation induced by changing light or glare. Thus, certain tasks in the current experiment may not show impairment while similar tasks were impaired reports when glare was involved or when smaller stimuli (requiring accommodation) were used. See previously published reports.

The subcritical tracking tasks that we utilized to anchor the other tasks essentially measure incoordination as well as ability to concentrate over time on the task. Incoordination has been demonstrated previously to be one of the manifestations of the atropine effect for doses ranging from 2 to 4 mg (1, 2, 4, 6).

Although the anchor task provides a contrast against which to view the impairment of the other tasks, caution is indicated in the interpretation that the lack of impairment effect for a given new task is due only to the lack of drug effect. Other factors, such as high performance variability induced by the drug treatment or even variability during the placebo session, must be considered. In some instances, there may even be an improvement in performance at the low doses, indicating a biphasic response to the drug that is not unlike the bradycardia/tachycardia biphasic response to low and high concentrations of atropine, respectively. Similarly, Miles et al. (5) found that atropine induced a faster reaction time to irregular stimuli in contrast to the regularly paced mode and timing of stimuli. The results for this

variable choice reaction time task indicated that compared to the simpler tasks, the supposedly "higher" mental operation was actually enhanced.

Lower doses have consistently produced variable results for cognitive tasks. Robinson (6) reported little deficit on a visual search masking task after a 2 mg dose. Mazulli and Cobe (4) giving 2 or 3 mg doses observed no difference in the performance decrements on a subtraction task, speed in reading, and digit recall tasks. Weatherill (7) interpreted his results as suggesting that the information storage function of memory rather than the retrieval process was impaired. The task used was a paired associate task in which both free and associative recall of word lists were required. In another study, Miles et al. (5) found that the visual reaction time, but not the simple auditory reaction time, tasks were impaired.

Headley (3) succinctly summarizes the state of the art and concludes that, "the extent of our knowledge in the cognitive psychopharmacology of atropine is not sufficient." He goes on to discuss the following points about the ability to monitor radar, to operate tracking weaponry, and to process and communicate information: 1) these are critical military skills for which it is very important to know the underlying skills required and 2) it is essential to understand their sensitivity to atropine dosing as well as the time course of the drug effect in order to predict at what doses personnel will be impaired and the duration of this impairment for specific tasks.

Methods and Data Analysis

In a dose response study, two single doses of placebo, 1.0, 2.0 or 4.0 mg of atropine were injected I.M. to 16 healthy males. Description of the task procedures and analysis of data can be found in the Appendix. Dosing and subject methodology procedures are the same as presented in previous reports. In contrast to the standardized battery tasks of earlier studies, many of the new tasks demonstrated considerable variability across time during the placebo condition. This variability was magnified under the low-dose conditions. On perusal of the data structure it was obvious that six subjects demonstrated such sufficiently marked variability during the placebo and low-dose conditions on almost all of the new tasks that an assessment of any dose response effect was rendered uninterpretable. In order to provide a better perspective for the evaluation of the actual atropine pharmacodynamic effect, the six subjects were excluded because of their high placebo condition variability. The placebo performance of the 10 remaining subjects on the anchor subcritical tracking task was noted to be a very consistent and reproducible.

Results

Figure 1A, 1B and 1C illustrate the dose response nature of the effect of atropine on the subcritical tracking task anchor variable. For the higher dose the impairment effect did not return to the pre drug baseline level until after 400 minutes. The level of difficulty for the subcritical tracking task is indicated by lambda 2, 3 and 4 and demonstrates that the higher level of difficulty provides a systematic exposition of the dose response condition. Thus, the tracking scores with their low placebo condition variability and

ATROPINE PHASE II
SUBCRITICAL TRACKING

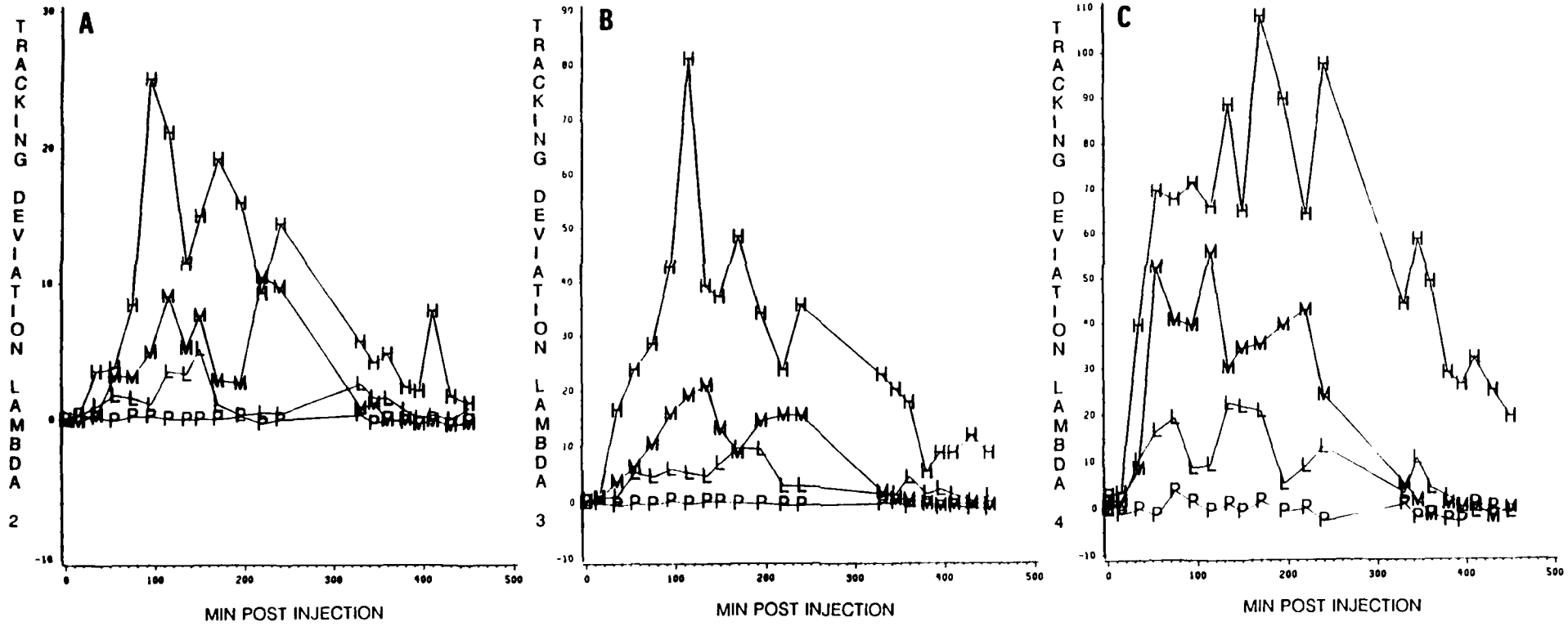

Figure 1. P = Placebo, L = 1.0 mg dose, M = 2.0 mg dose, and H = 4.0 mg dose.

robust dose response effect provide a solid reference standard for assessing the sensitivity of the other tasks to atropine.

Two new coordination tasks were assessed; i.e., the pendulum sway and rapid hand alternation tasks. The pendulum sway required the individual to manipulate his body balance in order to maintain a changing tracking condition which was presented on the TV projection screen. A platform transducer controlled a small circular cursor that the subject was required to keep between two constantly undulating parallel lines. The task, thus, required a fine sense of eye-postural mobility coordination and went beyond the requirements of just maintaining a steady static posture. The maximum and average deviation from the ideal tracking, are presented in Figures 2A and 2B. The plot of average deviation indicates that performance on pendulum sway was not affected until the 4.0 mg dose was administered. The placebo curve suggests that the subjects become better at this task during the test session even though subjects were trained to a plateau level of performance before drug testing. The maximum deviation data provide evidence that atropine may, in fact, improve body sway at the 2.0 mg dose. Because of the high variability of task performance, however, this remains only a suggestion.

The next task, rapid hand alternation, involved a requirement that the subject rapidly pronate and supernate his right hand while holding a handle transducer to provide a measure of speed of rapid alternation. The high dose indicates a reduction in capacity that shows a progressive increase over time. Mean scores were very stable throughout the test session, however, the low dose appears to induce an improvement in performance. Again, these are only suggestive findings, but the stability of the placebo condition and the marked contrast between the high and the lower doses would indicate that, depending on drug dose, there may be a biphasic response characterized by improvement at lower doses and impairment at high doses (Fig. 3). (Whether these outcomes are related to the well-known antiparkinsonian-like effect of atropine at low doses is an interesting conjecture that deserves further investigation.)

In other new tasks, fast eye movements were tested both with a saccade as well as a rapid eye alternation task. The saccade task required that the individual focus the visual cursor target on his fovea as rapidly as possible at various times. The cursor moved randomly between either 30, 35 or 40 degrees of the visual arc. In Figures 4A, 4B and 4C saccade velocity and saccade duration are presented for the four dose conditions. Only the high-dose condition induced significant impairment.

The rapid eye alternation task simply required that the individual alternate between two visual targets placed at a distance of 30 degrees of the visual arc. In Figures 5A and 5B, samples of this activity are presented and indicate that impairment is noted just for the 4 mg dose. Samples of the average velocity and number of cycles completed show similar profiles.

The number recall task is a fairly complicated procedure that attempts to sort out the recall versus recognition aspect of memory. Because the procedures are more complicated, details of the presentation of the number task are presented here and include:

ATROPINE PHASE II
PENDULUM SWAY TASK

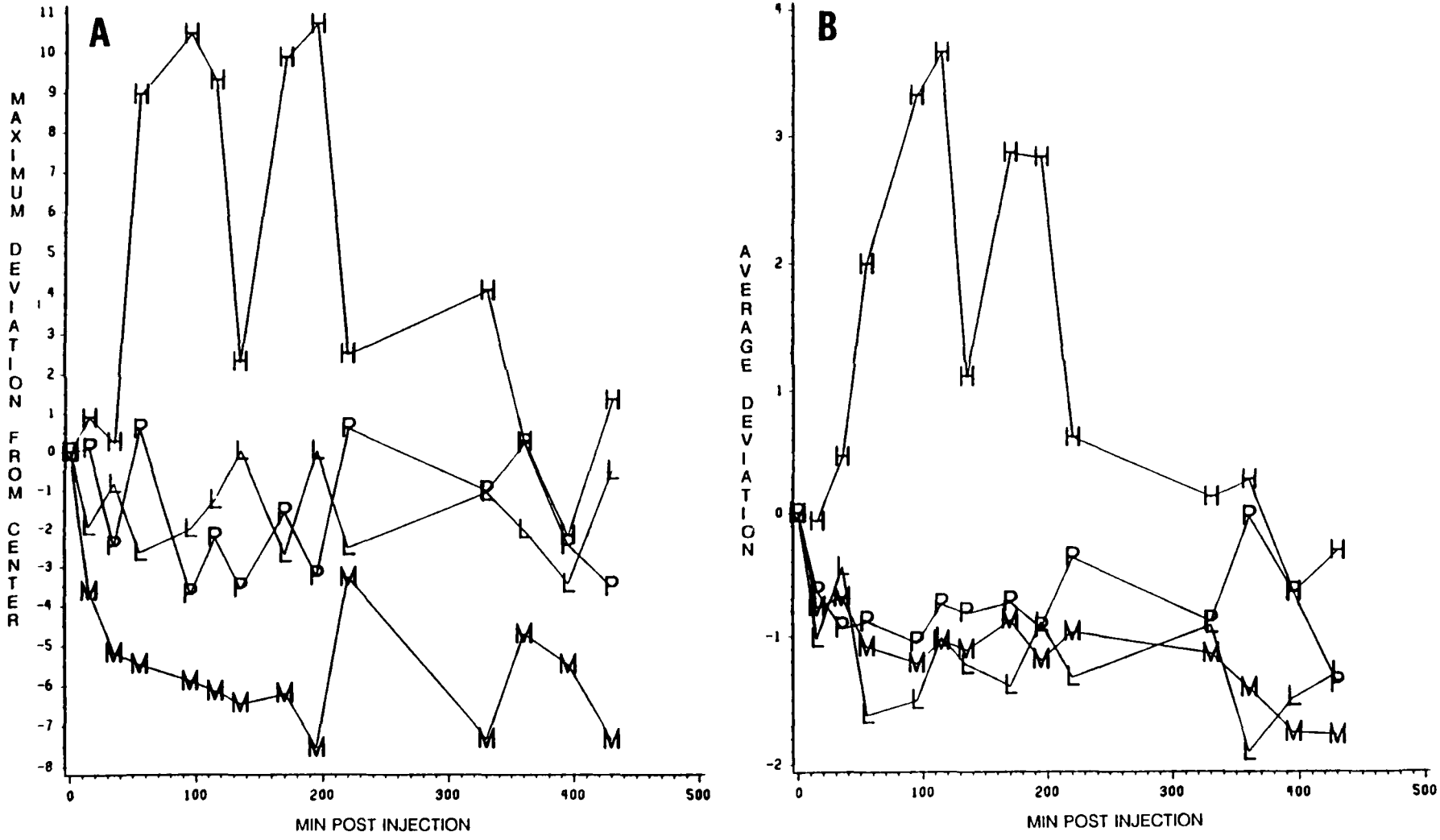

Figure 2. P = Placebo, L = 1.0 mg dose, M = 2.0 mg dose, and H = 4.0 mg dose.

ATROPINE PHASE II
HAND ALTERNATION TASK

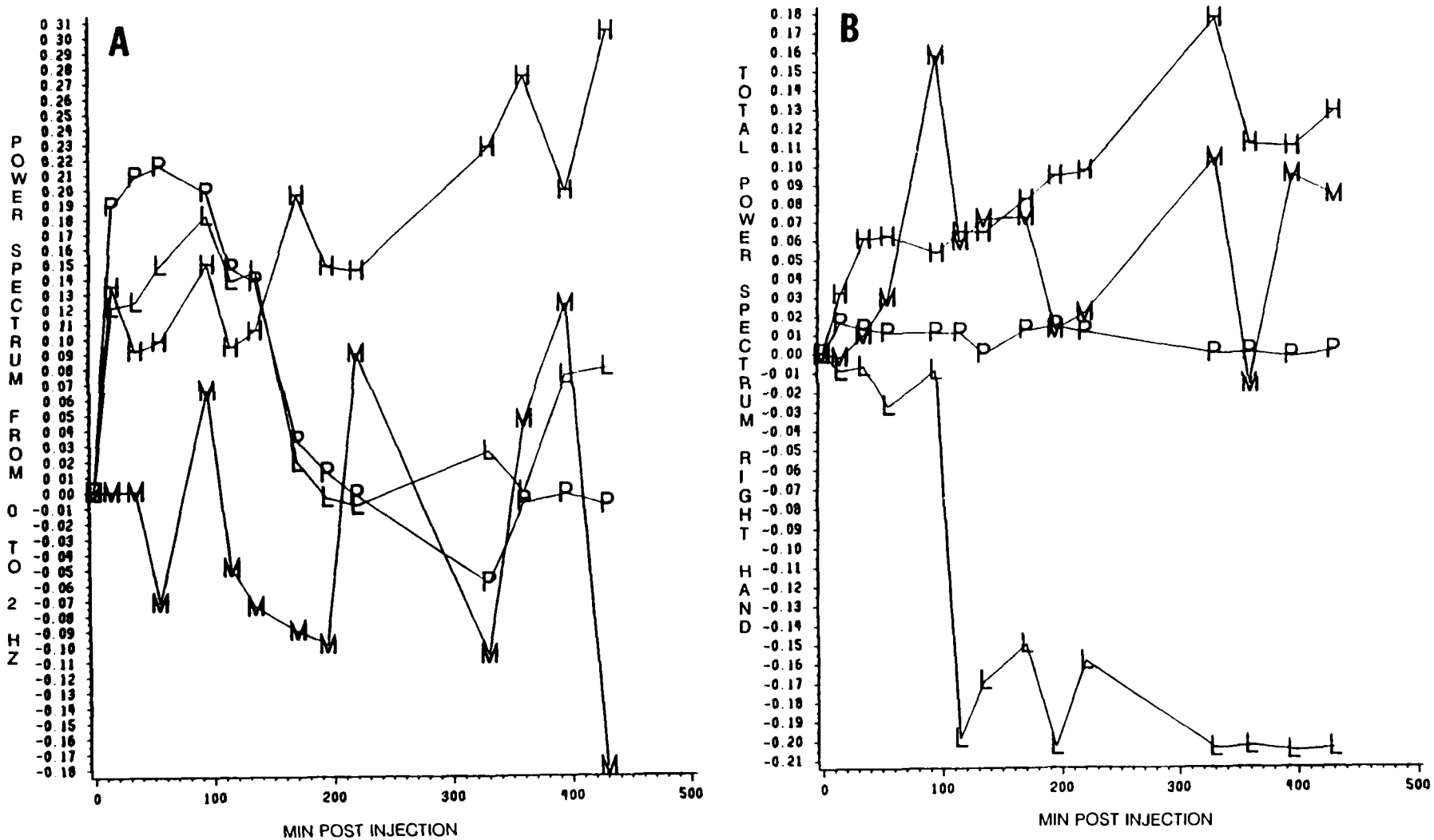

Figure 3. P = Placebo, L = 1.0 mg dose, M = 2.0 mg dose, and H = 4.0 mg dose.

ATROPINE PHASE II
SACCADE EYE TASK

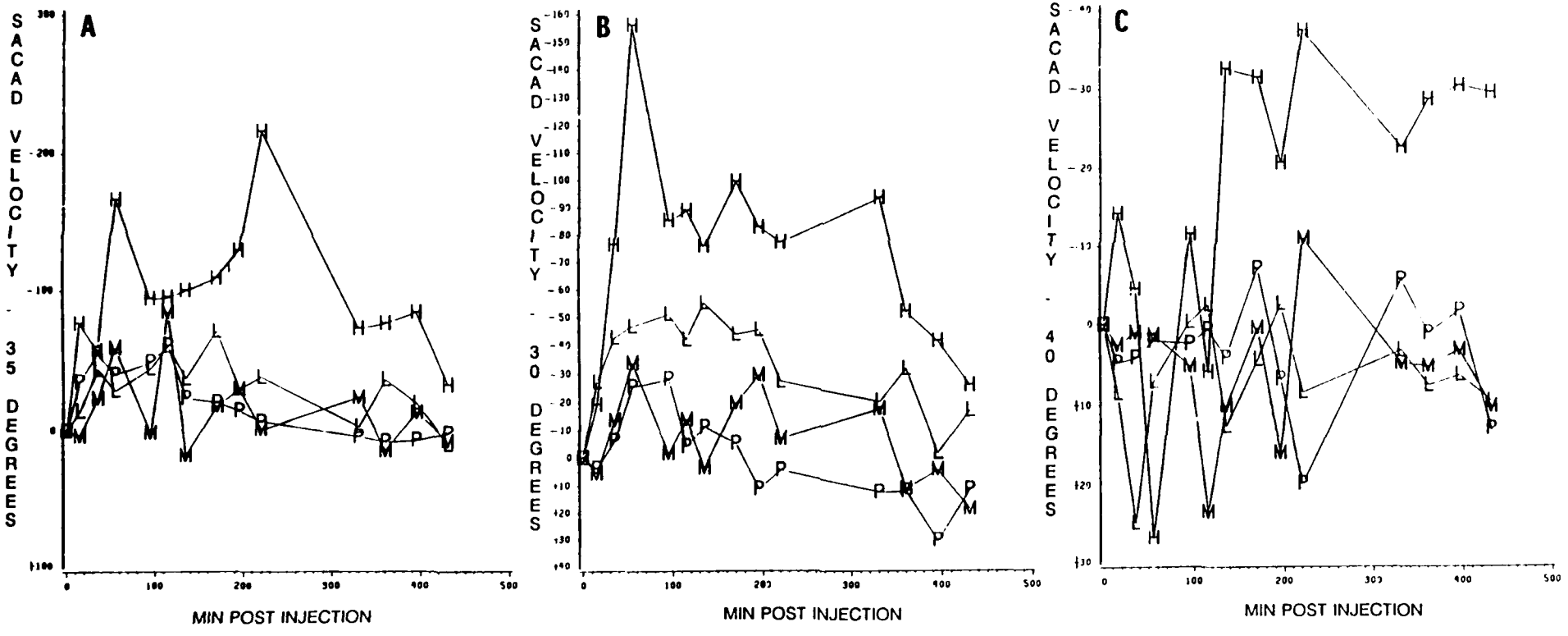

Figure 4. P = Placebo, L = 1.0 mg dose, M = 2.0 mg dose, and H = 4.0 mg dose.

ATROPINE PHASE II
RAPID EYE ALTERNATION TASK

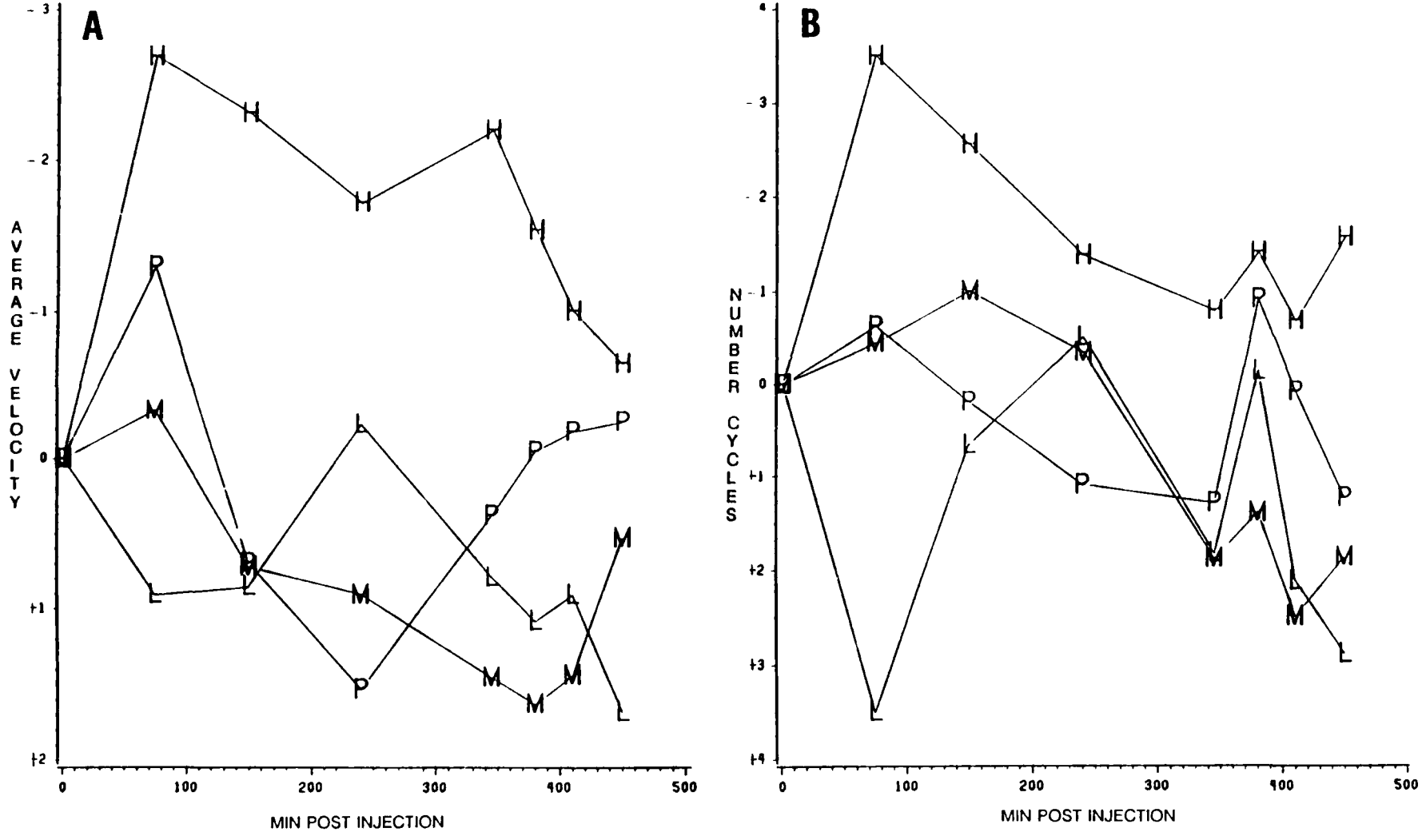

Figure 5. P = Placebo, L = 1.0 mg dose, M = 2.0 mg dose, and H = 4.0 mg dose.

Memory For Number Series Task

Apparatus

The stimulus set for the learning and recognition trials consisted of a single row of numerals. The number of digits in Sets 1, 2, 3, 4 and 5 were 1, 3, 5, 7 and 9, respectively. The stimulus sets for the learning trials were constructed as follows at the beginning of the task: the numerals to be used were randomly selected from the pool of single digits, 1 to 9; the sequence of the digits in each set was be randomly determined. The sets for the recognition trials are described in the procedure section.

Procedure

Learning Trial:

The stimulus set was displayed in the upper half of the screen for 15 sec. During this period the subject tried to memorize the sequence of numbers.

Free Recall Trial:

The stimulus set for the learning trial was erased from the screen. The subject was instructed to press on the keypad, one at a time, the sequence of numbers just learned in the same order presented during the learning trial. If the subject committed any errors in either the recall of the numeral or the sequence, the same learning set was presented a second time and was followed by a second recall trial. If necessary, learning sets were given a total of three times.

Recognition Trial:

Depending on the length of the learning set, a series of recognition stimulus sets was projected onto the screen after the final recall trial. For each recognition stimulus set presented, the subject was instructed to decide whether or not that particular number sequence was included in the learning set. If his response was "yes," he pressed "1" on the keypad and if his response was "no," he pressed "3" on the keypad.

Half of the recognition stimulus sets were correct and half were incorrect. The correct recognition sets consisted of subsets of the learning set. The incorrect recognition sets were the same length as the correct ones, but either the numbers or the sequence differed from the number sequence presented during learning. Therefore, the length of the recognition sets used with the different learning sets were as follows: recognition sets of 1 numeral for learning sets of 1 or 3 numerals; recognition sets of 1 and 3 numerals for learning sets of 5 numerals; recognition sets of 3 and 5 numerals for learning sets of 7 numerals; recognition sets of 3, 5 and 7 numerals for learning sets of 9 numerals. In order to reduce the number of repetitions in the number sequences of the recognition sets for all learning sets with 5 or more digits, all possible correct sequences were determined for the recognition sets. Half of these were used for the correct trials and the rest

were transformed into wrong trials by changing one or more of the digits or the order of the numerals. The order of right and wrong recognition trials was randomized. Finally, the initial and final digits were used on one or a maximum of two recognition trials per learning set (for all sets greater than 1 numeral).

Final Recall Trial:

After the subject completed the recognition trials, he was again required to press on the keypad the entire learning set in the correct order.

Analysis

The number pressed on the keypad and the reaction time (i.e., time interval from one response to the next) were recorded by the computer for the free recall trials. Subsequent analysis calculated for each recall test: the total number of correct responses, the average reaction time for the correct and incorrect responses, and the standard deviation for each mean reaction time. For the recognition test, the response measures were the number correct, number of false positives, the average reaction times for the correct and the false positive responses, and the standard deviation for each mean reaction time.

Results

The data of the number task were assessed in a number of different ways. In this section of the report we will only present the power scores for the number task, i.e., the number correct divided by the reaction time required. The details of the reaction time and the number correct measures can be found in the Appendix. The overall recall for the number task provides a suggestion of an impairment for the high dose. Examination of the sequential recall time periods are presented in the quartile displays of Figures 6A thru 6E. As with the recall task, recognition task also demonstrated no systematic dose response effect, and we have concluded that this task is a poor means of demonstrating either recognition or recall memory in the atropine condition. This is in spite of the fact that there is a reasonable plateau baseline curve for the placebo condition. The details of the reaction time and number of correct can be perused in Figures 7 to 11.

Summary

In comparison to the anchor variable (subcritical tracking) pendulum sway, saccade eye task, and rapid eye alteration task demonstrate limited promise as a task to measure atropine induced impairment. None of the tasks is as stable or robust in demonstrating systematic dose response effects as subcritical tracking. At this point, we would not recommend further development of these new alternative tasks for testing atropine effects.

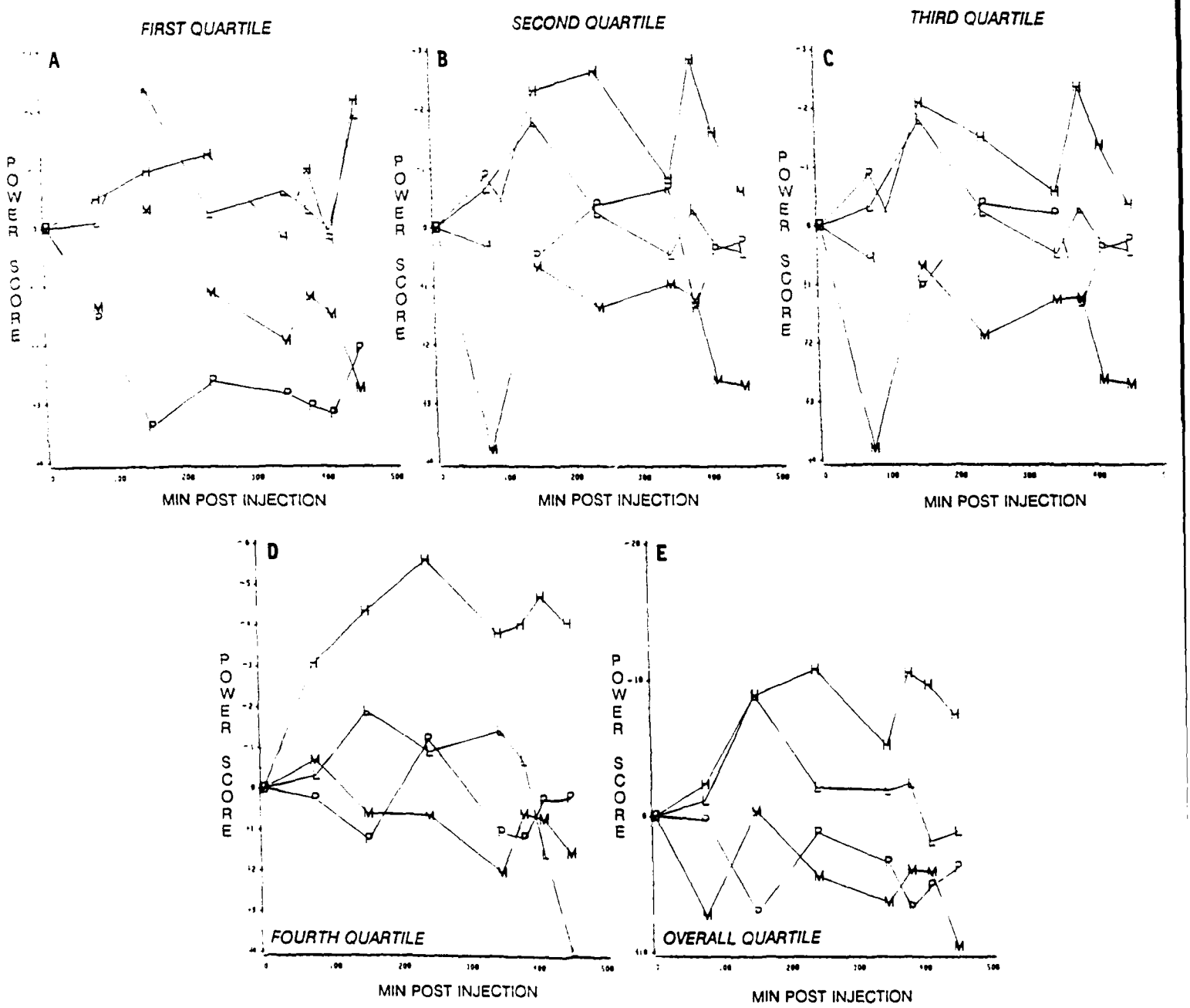

Figure 6. P = Placebo, L = 1.0 mg dose, M = 2.0 mg dose, and H = 4.0 mg dose. Power = Number correct divided by reaction time,

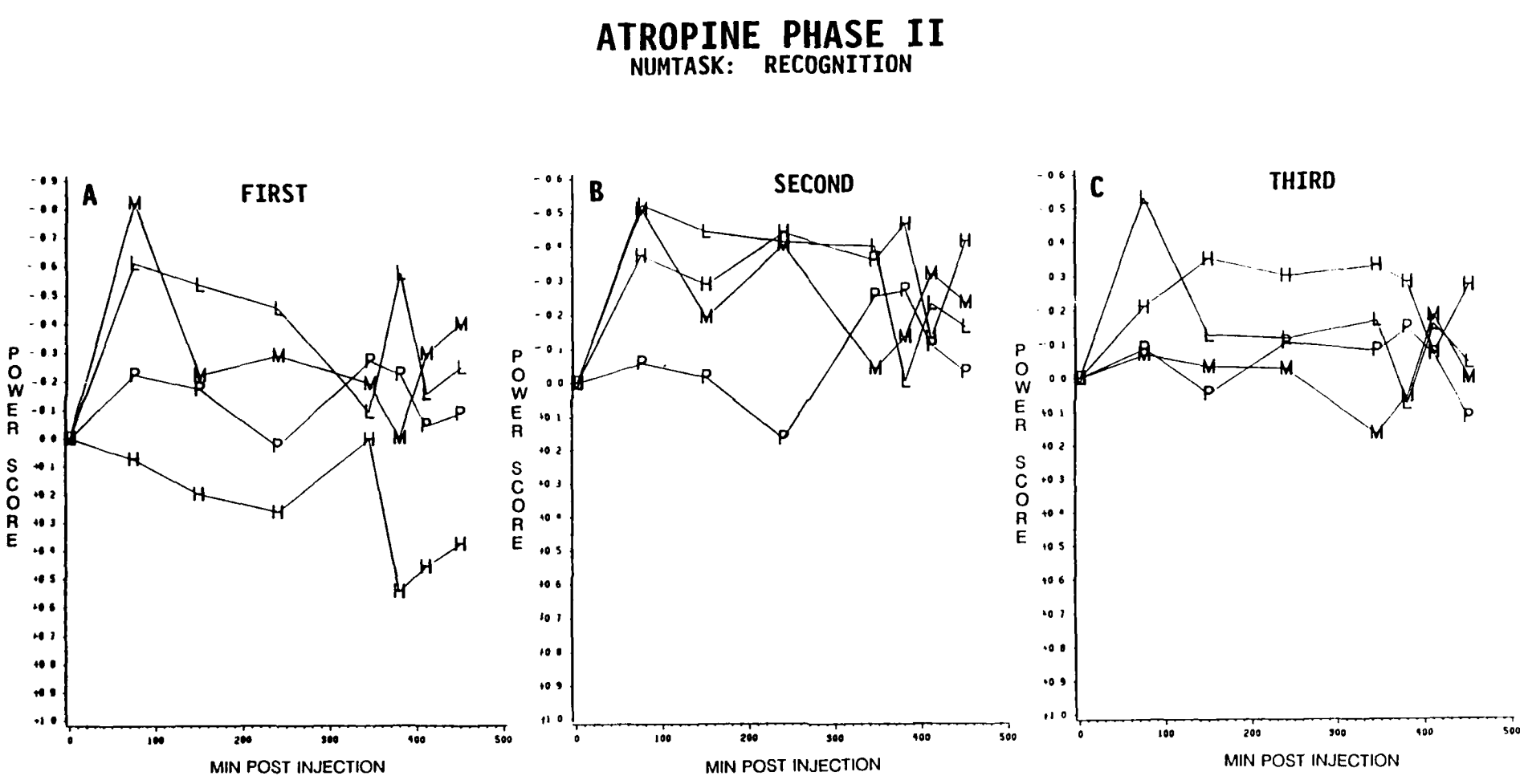

Figure 7. P = Placebo, L = 1.0 mg dose, M = 2.0 mg dose, and H = 4.0 mg dose.

ATROPINE PHASE II
NUMTASK: RECALL RT

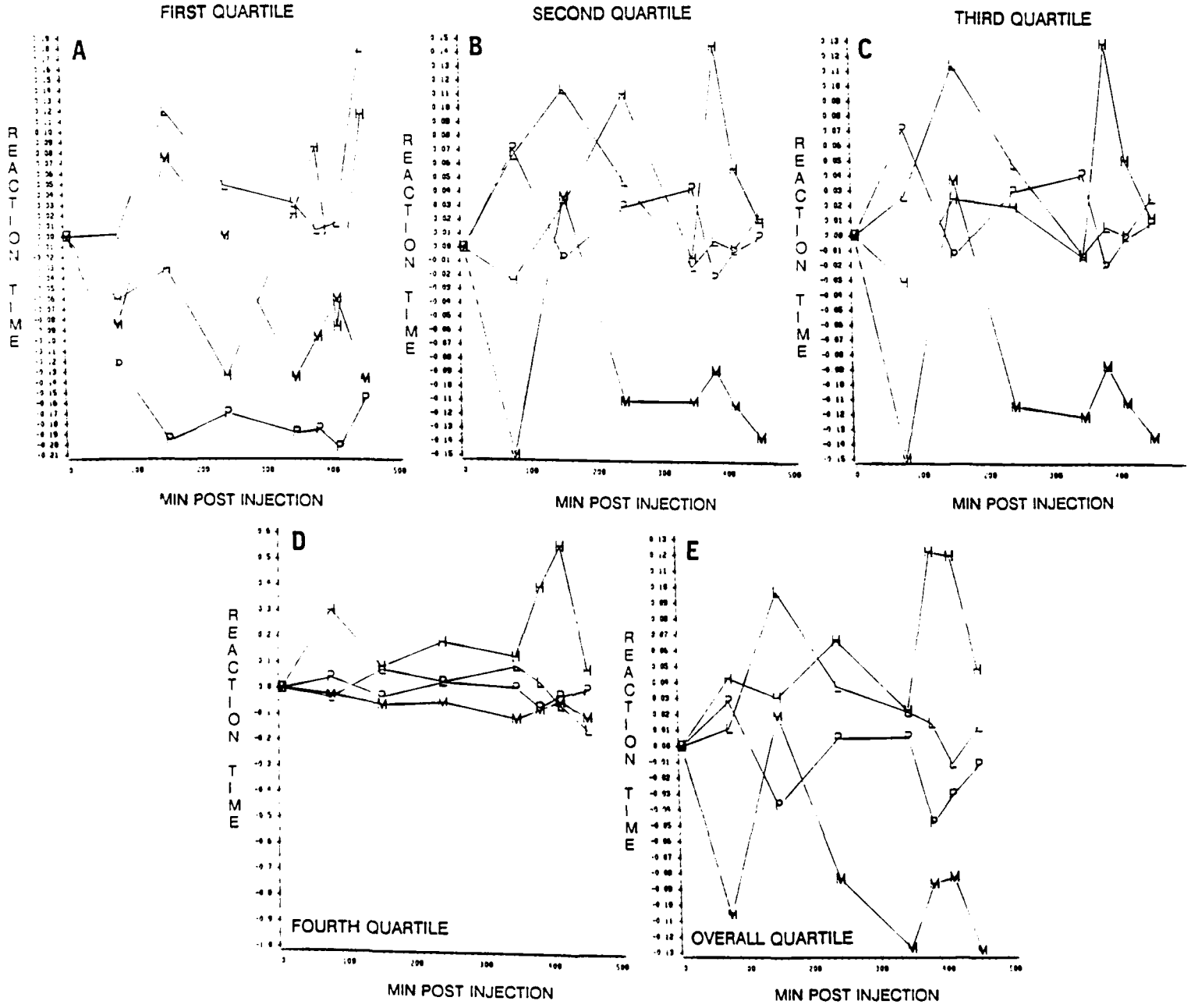

Figure 8. P = Placebo, L = 1.0 mg dose, M = 2.0 mg dose, and H = 4.0 mg dose.

ATROPINE PHASE II
NUMTASK: RECOGNITION RT

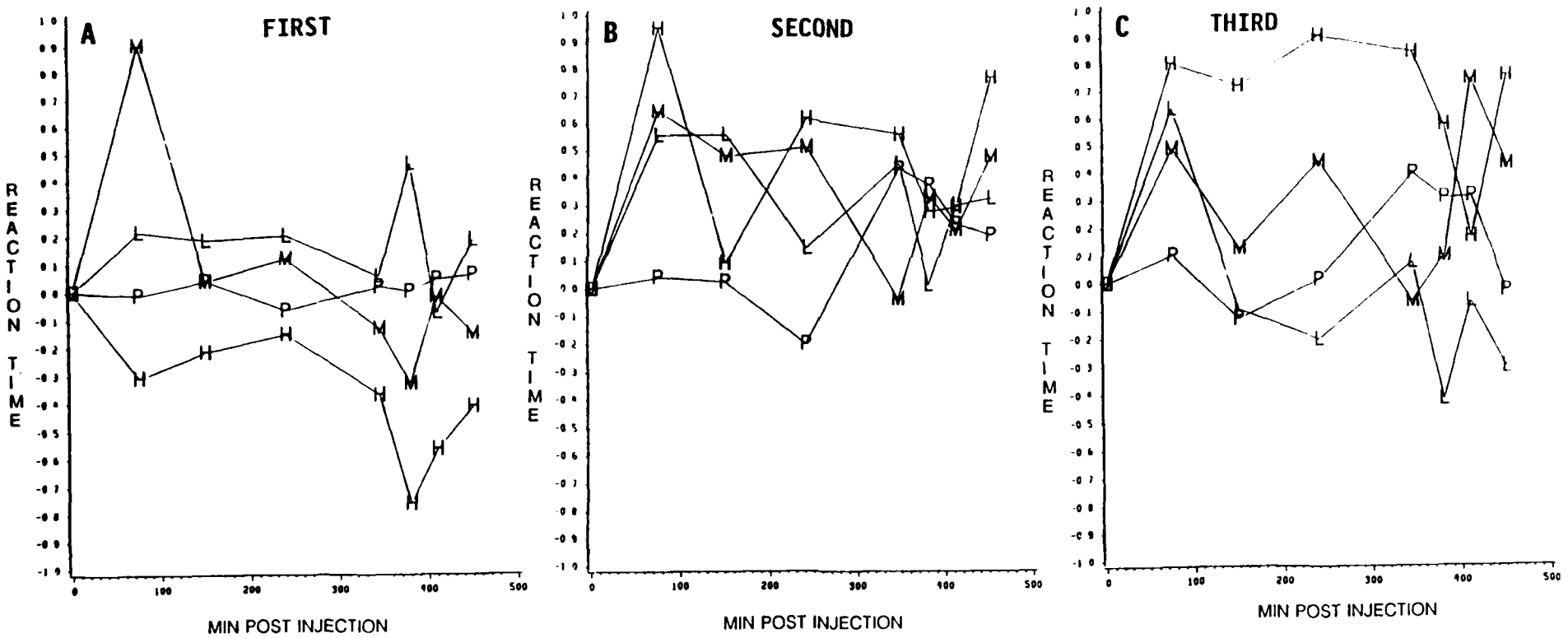

Figure 9. P = Placebo, L = 1.0 mg dose, M = 2.0 mg dose, and H = 4.0 mg dose.

ATROPINE PHASE II
NUMTASK: RECALL NC

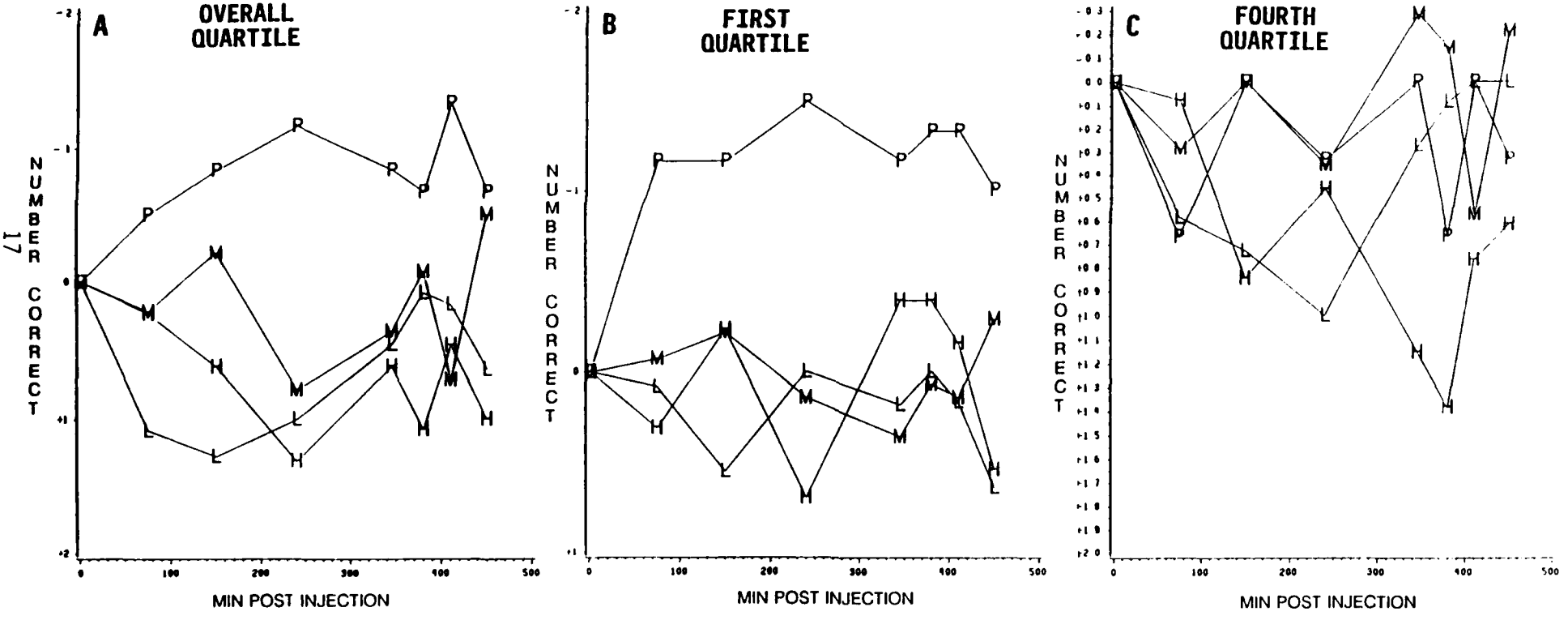

Figure 10. P = Placebo, L = 1.0 mg dose, M = 2.0 mg dose, and H = 4.0 mg dose.

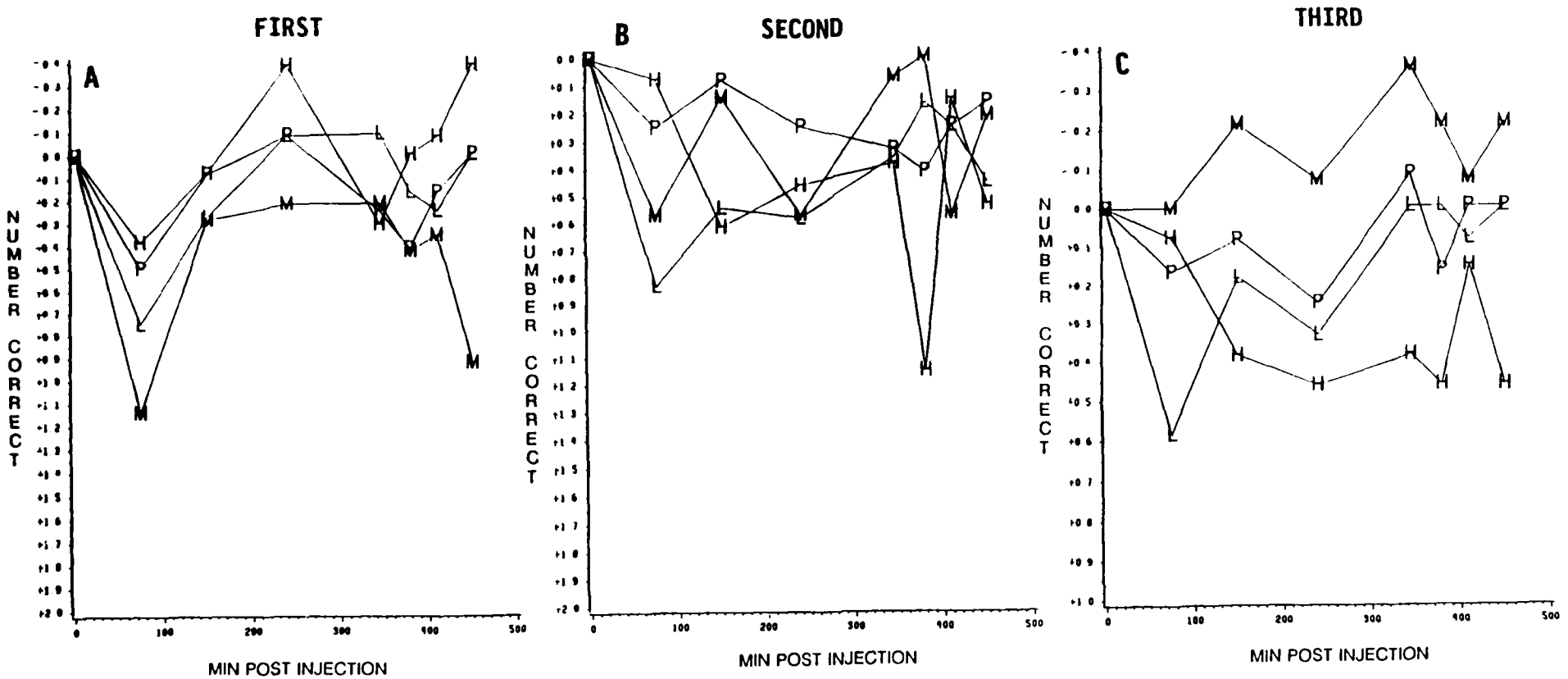

Figure 11. P = Placebo, L = 1.0 mg dose, M = 2.0 mg dose, and H = 4.0 mg dose.

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APPENDIX A

Schedule of Testing

TESTING PROCEDURE FOR ATROPINE STUDY
PHASE II

SUBJ_____
DATE_____
COND_____

TIME	TIME	BATT	PROCEDURE	SAMPLE
7:30			Arrival, range evaluation and breakfast	
7:40			Self-evaluation (SE)	
7:45			Catheter and hookups	
8:15	-1:00	01	BATMA	
8:35		02	BATMB	
9:00			BS 1, BP, HR, Temp	0 min
9:05			Noun Memory Trial 1	
9:15	**:00**		**DRUG ADMINISTRATION**	
9:25	:10		BS 2	10 min
9:30	:15	03	BATMA	
9:35	:20		BS 3, BP, HR, Temp after PENSWY	20 min
9:50	:35	04	BATMA,SE	
9:55	:40		BS 4, BP, HR, Temp after PENSWY	40 min
10:10	:55	05	BATMA,SE	
10:15	1:00		BS 5, BP, HR, Temp after PENSWY	60 min
10:30	1:15	06	BATMB,SE	
10:35	1:20		BS 6, BP, HR, Temp after PENSWY	80 min
10:50	1:35	07	BATMA,SE	
10:55	1:40		BS 7, BP, HR, Temp after PENSWY	100 min
11:09	1:54		Noun Memory Trial 1	
11:10	1:55	08	BATMA,SE	
11:15	2:00		BS 8, BP, HR, Temp after PENSWY	120 min
11:28	2:13		Noun Memory Learning Trial 2	
11:30	2:15	09	BATMA	
11:45	2:30	10	BATMB	
12:00	2:45		BS 9, BP, HR, Temp after BATTERY	165 min
12:05	2:50	11	BATMA	
12:25	3:10		BS 10, BP, HR, Temp after BATTERY	190 min
12:30	3:15	12	BATMA,SE	
12:50	3:35		BP, HR, Temp after Noun Memrory Recall Trial 2	
12:55	3:40	13	BATMA	
1:15	4:00	14	BATMB	
1:30	4:15		BS 11, BP, HR, Temp after BATTERY	255 min
1:35	4:20		LUNCH	
2:05	4:50		BP, HR, Temp	
2:45	5:30	15	BP, HR, Temp before BATMA	
3:00	5:45	16	BATMB	
3:15	6:00	17	BATMA	
3:30	6:15		BS 12, BP, HR, Temp after BATTERY	375 min
3:35	6:20	18	BATMB,SE	
3:50	6:35	19	BATMA	
4:05	6:50	20	BATMB	
4:20	7:05		BS 13, BP, HR, Temp after BATTERY	425 min
4:25	7:10	21	BATMA	
4:45	7:30	22	BATMB,SE	
4:55	7:50		Noun Memory Recall and Recognition Tasks	
5:00	7:55		Catheter and hookup removal, subject check, cleanup	

BATMA= PENSWY, HAND, TRK, SACAD4, PUPILOMETER
BATMB= TREMOR, FINGER, TRK, RAPEYE, NUMTSK

APPENDIX B

Description of Tasks

COMPUTERIZED COGNITIVE-NEUROMOTOR TASK BATTERY: DESCRIPTION OF PERFORMANCE TASKS AND ANALYSIS PROCEDURES

General Introduction

The following sections describe operating procedures, equipment and system verification and checkout, plus other aspects of using a computerized cognitive-neuromotor task battery to assess a variety of mental and motor skills in individuals.

System Description

The system consists of the equipment described below. Illustrations of the equipment are found in Figures 1, 2, 3 and 4 (Note: all figures are located at the end of this section).

Central Processor Unit (CPU) and Related Peripherals

This includes the PDP-11/34 computer, hard disc drives, TU80 magnetic tape system, a Decwriter terminal, and a video terminal. The video terminal is located in the anteroom of the test chamber. The Decwriter terminal, disc drives, and TU80 tape system are located beside the computer. A MAC panel mounted in the computer console allows programming of analog inputs, control lines, and other communications with the test chamber devices. The CPU and its associated equipment provide control for presentation of stimuli, accept analog inputs for digitization and subsequent processing, and perform data analysis and reduction tasks. Mass storage of collected data is performed by using the hard disks for short term storage, and by using magnetic tapes for bulk, long-term storage. The CPU operates under an RT-11 real time operating system.

Graphics Interface and Projector

This subsystem consists of a special purpose interface, manufactured in house, and a video projector. The interface accepts control signals from the PDP-11 and generates video signals which are routed via coaxial cable to the projector. Figures generated include numerals, symbols, and lines. In addition, these figures are capable of being manipulated; i.e., moved, flashed on and off, etc. The video projector displays these items on a 98 cm high x 128 cm wide translucent rearview screen for viewing by the subject.

Test Apparatus

The test apparatus consists of a chair with appropriate fixtures attached, including a steering wheel, a keypad for entering numeral and other responses, and a foot switch. In addition, a sway table for transducing body movements, plus amplifiers and pen recorders for eye movements are installed in the test chamber or anteroom.

System Operation

In use, the CPU performs all program control and data acquisition functions for the tasks, except for the recording of some analog data. Indirect command files are used to perform desired sequences of tasks, the nature of which are defined by the programs scheduled by the indirect command file. New tasks may be easily added or old ones deleted by modification of the indirect command files. Thus, a particular sequence of tasks may be performed by invoking the appropriate indirect command file. Individual tasks may be performed by running a single program. Once begun, the sequence of stimuli presentation, data measures, etc., are under computer control and require no operator intervention.

System Software

In addition to the RT-11 operating system, a number of application programs have been written to perform the following tasks.

Involved in the development of the computerized task battery over the last few years, has been the streamlining of equipment and transformation into systems that run on smaller computers. First, we downloaded the system to a PDP-11/23 version; subsequently, an IBM-PC version has been developed for all of the balance tasks, tracking tasks, and keyboard based tasks. This IBM system is described below.

System Description

The IBM-PC system consists of the equipment described below.

Central Processor Unit (CPU) and Related Peripherals

This includes the AST Premium/286 computer, with a 30 Mb disc drive, and a 30 inch NEC multisync video monitor. The computer is located in the anteroom of the test chamber. A Data Translation DT2801 data acquisition board mounted in the computer allows programming of analog inputs, control lines, and other communications with the test chamber devices. The CPU and its associated equipment provide control for presentation of stimuli, accept analog inputs for digitization and subsequent processing, and perform data analysis and reduction tasks. Mass storage of collected data is performed by the disc for short term usage, and by magnetic media for bulk, long-term storage. The computer is PC-AT compatible, and uses the MS-DOS operating system.

Graphics Interface and Projector

This subsystem consists of a Matrox PG-640 Professional Graphics interface, mounted in the AST, and a large screen NEC multisync monitor. The interface accepts control commands from the AST and generates video signals which are routed via a video cable to the monitor. Figures generated include numerals, symbols, and lines. In addition, these figures are capable of being manipulated; i.e., moved, flashed on and off, etc.

System Software

All application programs were written using MicroSoft's Macro assembler, C compiler, and Fortran compiler.

PENDULUM SWAY TASK

Apparatus

The sway table has been described in the previous section, Standing Steadiness Task. The display screen is also used in this task to provide task stimuli and visual feedback to the subject about his performance. After a 5 sec calibration period, two parallel lines are drawn in the center of screen and an "+" is displayed to mark the center. As the subject sways on the table his current position is reported on the screen by a "+".

Instructions

This test will measure your ability to control lateral sway movements with visual feedback of how well you are doing. The procedure is the same as Standing Steadiness Task, except the object is to keep the "+" on the screen as close to the center of the between the two lines as possible by making slight shifts in body weight. The two lines are moving side-to-side across the screen with a cyclic period of approximately 2.5 seconds.

Procedure

The subject positions himself on the sway table as in the Standing Steadiness task except that he faces the display screen instead of looking at a designated point. The subject is instructed to hold as still as possible for 5 sec, during which time the sway table self-calibrates. A mean x-y position of the subject's center of gravity is determined. Following the calibration the circle and "+" are drawn on the screen such that they appear centered on the screen, and are correspondingly centered over the subject's mean center of gravity. All measurements are recorded as deviations from the subject's mean center and are displayed on the screen as deviations from the center of the circle. In this fashion the screen acts as a mobile window that is centered over the subject's center of gravity which is determined from the calibration. The task lasts for 60 sec and all data are recorded and stored.

Analysis

The measures of merit are: mean x (port-starboard), mean y (fore-aft), mean deviation from center and maximum deviation from center.

TRACKING TASK

Apparatus

A 3 cm wide bar is displayed from top-to-bottom in the center of the screen. A portion of the bar, 34 cm in length, moves right or left across the full width of the screen. The distance from the screen to the top of the wheel is 54 cm. The wheel, 54 cm in diameter, is connected to a 10 turn pot 10 K ohm variable resistor.

Instructions

The aim of this task is to maintain the moving bar in the center of the screen, in line with the fixed bars running from the top and bottom of the screen with the steering wheel which controls the position of the bar. If the bar moves to the right, for example, turn the wheel to the left or in the opposite direction; if the bar moves to the left of the center move the wheel to the right. As a hint to controlling the bar, attempt to change the wheel in a smooth motion rather than in a fast jerky motion. You are scored on this task by your ability to keep the tracking bar in the center of the screen.

Procedure

During the first five seconds the level of difficulty (lambda) increases to a value of two. The level of difficulty is multiplied by the steering input (position of the pot) and added to the position of the bar, resulting in the bar being repositioned. A simplified equation of this relationship is: Change in bar position = (bar position + pot position) x level of difficulty (lambda). A new bar position is calculated from this equation 60 times a second. For example, if the bar moves to the right of the center line, and the pot is not turned in the opposite direction, then the bar will move further to the right. If the level of difficulty is increased, the bar will be displaced at a higher rate. Data are recorded for three minutes.

Analysis

A subject's performance on the tracking task is analyzed both in terms of his success in maintaining the bar near the center of the screen, and in terms of the character of the steering inputs he makes. The square root of the mean squared error is quoted as a measure of tracking success both for easier and the more difficult halves of the task. Steering wheel motion is subjected to Fourier transformations and the power spectra condensed into bands one Hz wide. The lower three of these bands, which contain the bulk of the activity are examined usually for drug dependent variations.

SUDDEN DISPLACEMENT SACCADE TEST

Apparatus

A dot is displayed in the center of the screen 39 cm from the top of the screen. The subject rests his chin in a molded chin rest located 84 cm from

the screen and in line with the center of the screen. Four cup-shaped, Beckman Cap electrodes are connected to the subject's forehead to record EOG's from both eyes as well as each eye separately. The ground and reference electrodes are attached above the subject's nose; the other two electrodes to the outside of each eye, a little below the medial and lateral canthus. The electrodes are connected to a Grass amplifier with filter settings adjusted to: high frequency = 0.1 kHz, lo frequency = 0.1 Hz.

These Grass amplifiers, located in the experimental chamber, are used to amplify the signal to reduce artifact in transmission to the polygraph outside the chamber.

Instructions

Rest your chin in the chin rest. A dot will appear in the center of the screen and after a short pause will disappear and reappear to the left of the center. The dot will pause there for a moment and then reappear to the right in the same sudden fashion. Try to follow the bar as best you can with eyes only. Do not anticipate its movement as the length of time that it pauses at the center is random. The bar position will alternate left, right, left, etc..

Procedure

The dot position suddenly alternates left, right, left, right, etc. a total of 45 times. The positions are designed to force the subject to rotate his eyes 30, 35 and 40 degrees to the left and right of the center of his gaze. The ordering of the dot's angular positions is balanced across the task so that the dot will appear at each location an equal number of times. The dot disappears for a short pause of .5 secs before reappearing for a duration of 1.00 sec.

Analysis

The mean duration, response time, and peak velocity are calculated from the total number of saccades. Each saccade recorded is calibrated for EOG voltage eye-angle correspondence.

CONTINUOUS ALTERNATING SACCADIC EYE MOVEMENT TASK

Apparatus

Two bars 7 cm tall and 1.5 cm wide are displayed 39 cm from the top of the screen. Each bar is displayed 42 cm from the outer edges of the screen. A chin rest is anchored to the wall such that it is in line with the center of the screen and 84 cm away from it. Four cup-shaped, Beckman Cap electrodes are connected to the subject's forehead to record EOG's from both eyes as well as each eye separately. The ground and reference electrodes are attached above the subject's nose; the other two electrodes to the outside of each eye, a little below the medial and lateral canthus. The electrodes are connected

to a Grass amplifier with filter settings adjusted to: high frequency = 0.1 kHz, lo frequency = 0.1 Hz.

These Grass amplifiers, located in the experimental chamber, are used to amplify the signal to reduce artifact in transmission to the polygraph outside the chamber.

Instructions

Place your chin in the chin rest. You will observe a bar appear on the screen to your left. Keep your eyes on the bar until it disappears. When the bar reappears to your right, watch that one until it disappears. Shortly after that, two separate bars will appear on the screen in the same positions to the left and right as those you just saw. As fast as you can, move your eyes back and forth between the bars until they disappear. Be careful to move only your eyes and not your head.

Procedure

A bar first appears 12.5 degrees to the right of the subject's center line of gaze and remains there for 2 sec. During that time EOG data is collected and an average voltage is determined that corresponds to that angle of eye rotation. A second calibration bar subsequently appears 12.5 degrees left of the subject's center line of gaze. After calibration is complete, two bars appear 14 cm to either side of the centerline of gaze. This corresponds to a total of 25 degrees of eye rotation between the two positions. The program AKIN collects and records EOG data for 10 sec as the subject swings his eyes back-and-forth between the two bars.

Analysis

The data are analyzed for intersaccade lag time, saccade duration, and peak saccadic velocity.

HAND TREMOR TEST

Apparatus

The transducer is a radio frequency capacitance field type transducer. The radio frequency is generated between two copper plates 8 x 12 inches, which reside in a 16 x 16 x 16 inch cabinet. A hard rubber tube extends from the front of the cabinet to the area (field) between the two plates. Movements within the radio frequency field between the two plates are transduced into analog signals that are amplified and monitored on a grass model 78 polygraph.

Instructions

This device measures small movements in your hands. Place your hand into the tube with your thumb pointing upward and spread your fingers

(demonstrated to subject). Hold your hand as still as possible. This task will last two minutes.

Procedure

Prior to each experimental day's run, each transducer is calibrated using a saline-filled 30 ml glass bottle pendulum, set to the same arc and excursion. When necessary, sensitivity is adjusted to produce the same standard 1 cm deflections on the polygraph.

When the subject has his hand positioned properly in the tube, the experimenter begin collecting data. The data is sampled for a period of two minutes. Extraneous high voltage low frequency signals are filtered out through the low frequency filter on the polygraph. After several minutes, the subject is asked to remove his hand.

Analysis

The signal from the polygraph is substantially processed through an analog to digital conversion (128/second) and Fast Fourier transform is applied to provide spectral estimate of the movement frequency sampled over bands of 1 to 2 0 Hz. Usually only 1 to 14 Hz data are reported, as higher frequencies have very low power. For later data analysis, the first twenty seconds and last twenty seconds of every test run are discarded. The remaining data are divided into four epochs of 20 seconds each. The slope and mean intercept for each epoch for each frequency is assessed by growth curve analysis using SAS, (see Ellinwood et al., Pharm. Biochem. and Behav., 15:627-631, 1981, for a more complete description of the analysis). Drugs such as physostigmine caused an increase in 11-12 Hz tremor.

RAPID HAND ALTERNATION TASK

Apparatus

A potentiometer attached to a hand held toggle bar is used in this task. The variable voltages produced by supernating and pronating the toggle bar are treated as analog input to the computer for frequency analysis.

Instructions

You are to grasp the handle firmly and alternate it as rapidly as possible from one side to the other until told to stop. Next you are to alternate it as rapidly as possible, but this time forward and backward.

Procedure

The variable voltages are produced by rapidly supernating and pronating the toggle bar.

Analysis

The analog signal is sent through an analog to digital converter and subsequently peak frequencies for both side-to-side and forward-to-backward and determined by a Fast Fourier Transform program.

FINGER RAPID ALTERNATION TASK

Apparatus

Two Grass finger accelerometers are used in this task. One accelerometer for the middle finger of each hand.

Instructions

You are to oscillate both of your middle fingers as rapidly as possible. Remember you are to oscillate both fingers at the same time as fast as possible.

Procedure

The subjects rapidly oscillate both middle fingers, for 30 sec takes a pause, then again repeat the same movement.

Analysis

The dependent measure is the power spectrum produced due to movement of the accelerometers. The central frequency as well as a measure of power dispersion about the central frequency is estimated from the percent power at the frequencies in and about the central tendency. Percent power within 2 Hz of the central frequency will be measured. The baseline measure also provides another estimate of parkinsonian, essential physiological, and other tremor frequencies. This task produces data similar to the finger tapping task.

MEMORY FOR NUMBER SERIES TASK

This task is an adaptation of the Sternberg task (Sternberg, 1975) and uses the item recognition paradigm and reaction time measures to study various memory processes, including exhaustive-memory scanning and short-term memory. The computer programs for this task are under development.

Apparatus

The stimulus set for the learning and recognition trials consists of a single row of numerals. The number of digits in Sets 1, 2, 3, 4 and 5 are 1, 3, 5, 7 and 9, respectively. The stimulus sets for the learning trials are constructed as follows at the beginning of the task: the numerals to be used will be randomly selected from the pool of single digits, 1 to 9; the sequence of the digits in each set will be randomly determined. The sets for the recognition trials are described in the procedure section.

Procedure

Learning Trial: The stimulus set is displayed in the upper half of the screen for 15 sec. During this period the subject tries to memorize the sequence of numbers.

Free Recall Trial: The stimulus set for the learning trial is erased from the screen. The subject is instructed to press on the keypad, one at a time, the sequence of numbers just learned in the same order presented during the learning trial. If the subject commits any errors in either the recall of the numeral or the sequence, the same learning set is presented a second time and is followed by a second recall trial. If necessary, learning sets may be given a total of three times.

Recognition Trial: Depending on the length of the learning set, a series of recognition stimulus sets will be projected onto the screen after the final recall trial. For each recognition stimulus set presented, the subject is instructed to decide whether or not that particular number sequence was included in the learning set. If his response is "yes," he presses "1" on the keypad and if his response is "no," he presses "3" on the keypad.

Half of the recognition stimulus sets will be correct and half will be incorrect. The correct recognition sets will consist of subsets of the learning set. The incorrect recognition sets will be the same length as the correct ones, but either the numbers or the sequence will differ from the number sequence presented during learning. Therefore, the length of the recognition sets used with the different learning sets are as follows: recognition sets of 1 numeral for learning sets of 1 or 3 numerals; recognition sets of 1 and 3 numerals for learning sets of 5 numerals; recognition sets of 3 and 5 numerals for learning sets of 7 numerals; recognition sets of 3, 5 and 7 numerals for learning sets of 9 numerals. In order to reduce the number of repetitions in the number sequences of the recognition sets for all learning sets with 5 or more digits, all possible correct sequences are determined for the recognition sets. Half of these are used for the correct trials and the rest are transformed into wrong trials by changing one or more of the digits or the order of the numerals. The order of right and wrong recognition trials is randomized. Finally, the initial and final digits can only be used on one or a maximum of two recognition trials per learning set (for all sets greater than 1 numeral).

Final Recall Trial: After the subject has completed the recognition trials, he is again required to press on the keypad the entire learning set in the correct order.

Analysis

The number pressed on the keypad and the reaction time (i.e., time interval from one response to the next) are recorded by the computer for the free recall trials. Subsequent analysis calculates for each recall test: the total number of correct responses, the average reaction time for the correct and incorrect responses, and the standard deviation for each mean reaction time. For the recognition test, the number correct, number of false

positives, the average reaction times for the correct and the false positive responses, and the standard deviation for each mean reaction time will be the response measures.

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